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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,721	02/09/2004	Ralf Jockers	FRAV2003/0005USNP	9535

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
08/31/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/774,721	JOCKERS ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5/20/2009 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 5/20/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 1/2/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 5/20/2009, claims 49-54 are pending and examined herein.

Claim Rejections - 35 USC § 112, first paragraph (New matter)—withdrawn

The rejection of Claims 49-54 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 103—withdrawn

The rejection of Claims 12, 14, 15, 17, 47, and 48 under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (US Patent Application 2003/0166847); Agrawal and Tang (WO 94/01550); Taylor et al. (1999) *Drug Discovery Today* 4:562–567; Bennet et al. (US Patent 5,998,148); and Baracchini et al. (US Patent 5,801,154) is moot in view of the cancellation of the claims.

***

The rejection of Claims 12, 14, 15, 17, 47, and 48 under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (1997) *Nucleic Acids Res.* 25:2752-2758 in view of Tuschl et al. (US 2004/0259247 A1), Shi et al. (US 20030180756 A1), and Hannon (2002) *Nature* 418:244-251 is moot in view of the cancellation of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 49-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Akerblom "Human leptin receptor-related protein" (US Patent 5,789,198).

The claims are drawn to an antisense oligonucleotide "comprising" SEQ ID NO:2, and to vectors, host cells, and compositions thereof containing said oligonucleotide, vector, and cells.

The claims do not define or limit the length of the oligonucleotide and expressly include open "comprising" language. Therefore, the claims do not exclude additional, unrecited elements such as additional unrecited sequences flanking or contiguous with the recited sequence, SEQ ID NO:2. While the specification explains at pages 3 and 4 that sequences of 8 to 50 nucleotides are preferred, no clear or limiting definition is provided that would clearly restrict the length of the oligonucleotide as now claimed, and though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

Akerblom et al. disclosed the sense and antisense strands corresponding to a leptin receptor-related gene sequence (SEQ ID NO:2) that contains a nucleotide sequence that is 100% complementary to the instantly recited antisense oligonucleotide, SEQ ID NO:2 (see alignment below; and see cols. 2, 3 (lines 1-10), 18, and 25 (beginning at line 65)). Akerblom et al. further disclosed antisense oligonucleotides complementary to the leptin receptor-related gene sequence for inhibiting the expression of naturally occurring LRRP in cells in vitro and in vivo (cols. 2, 3 (lines 1-10), 18, and 25 (beginning at line 65)). At column 25, Akerblom et al. state the LRRP-encoding sequence, or any part thereof, is used to inhibit the expression of LRRP, reasonably implying that full or nearly full length antisense sequences may be used. In the next sentence, Akerblom et al. state "Although use of antisense oligonucleotides, comprising about 20 base-pairs, is specifically described, essentially the same procedure is used with larger cDNA fragments," again reasonably implying that long and possibly full length antisense sequences may be used. One of skill would instantly envision all such sequences based on the disclosure of the target gene, identified therein as SEQ ID NO:2 (LRRP). Such sequences would necessarily

"comprise" instant SEQ ID NO:2. (Akerblom does not disclose or suggest an antisense oligonucleotide "consisting of" instant SEQ ID NO:2).

At column 18, lines 55-65, Akerblom disclosed vectors that incorporate LRRP-specific antisense sequences for introduction into cells. Also disclosed are pharmaceutical compositions which would reasonably be used with any of the nucleic acid sequences, vectors, and cells disclosed therein (cols. 19-22).

Accordingly, Akerblom described antisense sequences, vectors, and host cells compounds and compositions within the scope of the instant claims.

```
>gb|AR020775.1|AR020775  Sequence 2 from patent US 5789198
Length=874

                                                                  Sort
                                                                    E v
                                                                    Qu

 Score = 40.1 bits (20),  Expect = 0.013
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1    AATGCCGCATGTGCACATGT  20
            ||||||||||||||||||||
Sbjct  540  AATGCCGCATGTGCACATGT  521
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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 49-54 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Akerblom "Human leptin receptor-related protein" (US Patent 5,789,198) in view of

1. Bennett et al. (1999) *Biochimica Biophysica Acta* 1489:19-30;
2. Vickers et al. (2003) *J. Biol. Chem.* 278:7108-7118; and
3. Bennett et al. (US Patent 5,998,148).

In the interest of compact prosecution, the following further rejection is applied wherein claim 49 is interpreted as being drawn to an antisense oligonucleotide "consisting of" SEQ ID NO:2. The instant rejection is rebuttable by objective evidence of unexpected properties of SEQ ID NO:2.

Akerblom is relied on for the reasons given above. Akerblom does not specifically describe the antisense oligonucleotide "consisting of" SEQ ID NO:2.

However, Akerblom disclosed at column 26, lines 12-16, that using an appropriate portion of the leader and 5' sequence of SEQ ID NO:2 (the LRRP sequence), an effective antisense oligonucleotide includes any 15-20 nucleotide spanning the region which translates into the signal or early coding sequence of the polypeptide as shown in FIGS. 1A and 1B. Reference to Figs. 1A and 1B shows that the nucleotide sequence shown therein, which is approximately 648 nucleotides in length, contains a 20-nucleotide sequence that is 100% complementary to instantly recited SEQ ID NO:2 (compare alignment above with the relevant portion shown in Fig. 1B). In view of this disclosure one of skill would reasonably have envisioned, by visual inspection or computer aided analysis, the complete list of 15-20-nucleotide antisense oligonucleotides complementary to the sequence shown in Figs. 1A and B. This list would necessarily have contained the instantly recited antisense oligonucleotide.

In view of this disclosure taken together with the disclosures of References 1-3, above, one of skill would have had reason to make and test as many antisense oligonucleotides in this list as feasible to identify those having the maximum inhibitory activity against LRRP with the reasonable expectation that the most if not all of the antisense oligonucleotides would inhibit the expression of LRRP to some degree. Furthermore, one of skill would have been able to immediately envision the instantly claimed olignucleotide from the genus suggested by Akerblom (MPEP 2144.08).

For example, Bennett et al. (1999) taught methods for designing and using antisense oligonucleotides to inhibit the expression of any known gene in vitro and in vivo (pp. 19-30). It is said that antisense oligonucleotides are ideal for gene functionalization and target validation studies; that antisense oligos are designed directly based on target sequence information; that

identification and validation of antisense inhibitors is rapid; and that the technology can be used for cell culture based assays and for complex in vivo models (page 20). At page 22, is said that antisense design is rapid and straightforward and may even be viewed as rational drug design. It is said antisense oligonucleotides can be designed directly from the genomic sequence information by simply making the reversed complement of the desired sequence. Bennett et al. recommend testing as many oligonucleotides as feasible to ensure that the most potent oligonucleotides are identified (page 23). Bennett et al. taught that high-throughput screening assays were available to facilitate this process (page 23). At page 27, Bennett et al. suggest using 2'-O-methyoxyethyl modifications to enhance the nuclease stability of the oligonucleotides.

As evidenced by Bennett et al. (US Patent 5,998,148), columns 38-39, making and testing 2'-O-methyoxyethyl modified antisense oligonucleotides was routine in the art. Bennett et al. (US Patent 5,998,148) is considered to be generally representative of the state of the art and level of skill of antisense technology, describing the materials and methods for making and using and benefits of using chemically modified antisense oligonucleotides of 8 to 30 bases and preferably 20 bases in length (col. 50). As shown by the data in Table 1, column 39, therein, it was routine to synthesize and test oligonucleotides against a number of different sites throughout the gene for their inhibitory activity. Thus, gene walking was routine, involving nothing more than preparing complementary 20-mers and assaying their relative activity using routine assay methods. As shown by the data in Table 1, the overwhelming majority of the antisense oligonucleotides targeting sites in the coding region of the gene inhibit expression. The data show that antisense activity varies as a function of target site, and that potency in vivo or in vitro is therefore directly dependent on target site, providing ample reason to make and test several oligos throughout the

gene coding region to identify those having optimum activity. In view of Bennett et al. (1999) teaching that activity in vitro depends, in part, on uptake efficiency, and that lack of efficient uptake in vitro does not predict lack of in vivo activity (page 23), and in view of the many different in vivo delivery vehicles available at the time of invention, one of skill would reasonably predict that many if not all the chemically modified oligos of a given gene walk would inhibit gene expression in vitro and/or vivo.

Bolstering these disclosures is Vickers et al., who also taught that gene-walking to confirm the activity and establish the relative potency of individual 20-nucleotide 2'-methoxyethyl/phosphorothioate modified (gapmer) antisense oligonucleotides targeting sites along a known mRNA sequence was routine in the prior art (see Results section showing results for two separate gene walks along the full length of two separate genes, Tables I and II, Figs. 3 and 4). Moreover, Vickers et al. showed that the vast majority of antisense oligonucleotides tested along the length of each gene inhibit the expression of the gene at some level (see Figs. 3 and 4). Vickers et al. recommend use of single stranded, 2'-methoxyethyl modified oligonucleotides of the type now claimed for research and therapeutic use in vitro and in vivo.

As a whole, then, the prior art reasonably suggested making and testing all possible 20-nt antisense oligonucleotides along the length of the ~648-nucleotide LRRP gene disclosed in Figs 1A-B by Akerblom to identify those antisense oligonucleotides with greatest inhibitory potency with the reasonable expectation that most if not all the chemically modified 20-nt antisense oligos tested would inhibit the expression of LRRP to some degree, albeit to different relative degrees depending on the site targeted, as shown by the prior art. Because the complete set of all possible 20-mers is finite and described by the target gene nucleotide sequence (i.e., by the

Watson-Crick base pairing principles), one of skill would have been able to immediately envision each candidate 20-nt antisense oligonucleotide in the genus (MPEP 2144.08). It is further noted that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success (MPEP 2143.02). In the instant case the prior art suggests that any of the 15-20-nucleotide antisense complementary to the LRRP gene in Figs. 1A and B of Akerblom will work, and that most antisense oligos tested along the length of a given gene inhibit the expression of the gene to some degree. The claims require nothing more.

Accordingly, the instantly claimed antisense oligonucleotides, vectors, cells, and compositions would have been prima facie obvious at the time of invention.

Response to Applicants' Arguments

Applicants' arguments presented on 5/20/2009 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
August 25, 2009